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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,401	07/31/2001	Shoshana Merchav	01/22310	1613

7590 04/09/2004

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EXAMINER
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NAFF, DAVID M

ART UNIT	PAPER NUMBER
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1651

DATE MAILED: 04/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/890,401

**Applicant(s)**

MERCHAV ET AL.

**Examiner**

David M. Naff

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 26 March 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-99 is/are pending in the application.
- 4a) Of the above claim(s) 21-50 and 71-99 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-20 & 51-70 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                                    |

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**DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/26/04 has been entered.

The amendment of 3/26/04 amended claims 1 and 51.

Claims 21-50 and 71-99 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 7 (filed 10/30/02).

Claims examined on the merits are 1-20 and 51-70.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Claim Rejections - 35 USC § 112***

Claims 1-20 and 51-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are confusing and unclear by claims 1 and 51 in line 1 of step (b) and (ii), respectively, reciting "the" undifferentiated hemopoietic stem cells or progenitor cells. While undifferentiated hemopoietic stem cells or progenitor cells are required in the

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preamble of claims 1 and 51, the cells have not been required in a previous step in the steps of carrying out the method. It is suggested that "the" be deleted.

***Claim Rejections - 35 USC § 103***

5        Claims 1-20 and 51-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al (5,541,107) in view of Sussman et al (5,266,476) and Stephanopoulos et al (5,510,262).

      Claims 1-20 are drawn to a method of expanding/maintaining undifferentiated hemopoietic stem cells or progenitor cells by  
0        culturing in a stationary phase plug-flow bioreactor a stromal cell culture under flow of a culture medium on a substrate in the form of a sheet including a non-woven fibrous matrix forming a three-dimensional network of fibers to generate a three dimensional stromal cell culture, and seeding undifferentiated hemopoietic stem cells or  
5        progenitor cells into the bioreactor including the three dimensional stromal cell culture.

      Claims 51-70 require a method of transplanting undifferentiated hemopoietic stem cells or progenitor cells resulting from expanding/maintaining the cells by the method of claims 1-20.

0        Naughton et al disclose growing stromal cells on a three-dimensional matrix which can be formed from a polymeric material to produce a three-dimensional stromal matrix (col 9, lines 16-20 and 49-51 and col 13, lines 8-14), inoculating the stromal matrix with stem cells (col 15, lines 41 and 57 and col 21, lines 3, 9, and 26) such as  
5        hematopoietic stem cells (col 21, line 3), maintaining the stem cells

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on the matrix *in vitro* where proliferation of the cells is maximized (col 21, lines 2-3), and implanting the stem cells *in vivo* to repopulate bone marrow (col 16, lines 58-67 and col 21, lines 4-5). Naughton et al additionally disclose (col 14, lines 45-50 and col 16, lines 24-30) continuously flowing fresh medium through the system at a rate of flow sufficient to replenish nutrients and maximize proliferation within the matrix, and to remove released cells so they will not stick to the vessel walls.

Sussman et al disclose a fibrous matrix for cell cultivation.

The matrix can be a non-woven fiber sheet (col 4, line 56), and can have a pore volume of 40-90%, a pore size of 10-100  $\mu\text{m}$ , a height of 50-500  $\mu\text{m}$ , and a fiber diameter of 0.5-50  $\mu\text{m}$  (col 2, lines 47-65). Matrix sheets can be used as a packing in a column (paragraph bridging cols 7 and 8) where medium flows through the column. The matrix can be coated with poly-D-lysine (col 13, line 68). The fiber sheet provides increased attachment surface for adherence of cells, and adequate porosity for entrance of cells and nutrients and for removal of wastes (col 4, lines 46-66)

Stephanopoulos et al disclose a cell-culturing reactor having an inlet and outlet for culture medium and containing a macroporous support between the inlet and outlet having pores of a size that allows cells to collect within the pores and oxygen and nutrients to migrate into the pores for consumption by the cells (paragraph bridging cols 2 and 3).

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When continuously flowing medium through a culture system containing a three-dimensional matrix on which stromal cells and hematopoietic stem cells are being cultured as disclosed by Naughton et al, it would have been obvious to provide a flow through system by using as the matrix the non-woven fibrous sheet of Sussman et al for its advantage of providing increased attachment surface for adherence of cells, and adequate porosity for entrance of cells and nutrients and for removal of wastes since the sheet can be used as a packing in a column for continuous flow of medium in cell culture, and as suggested by Stephanopoulos et al teaching cell culture using a continuous flow reactor containing a packed bed of substrate particles on which cells are grown, and an inlet and outlet for continuous medium flow.

### ***Response to Arguments***

Applicants have presented a 37 CFR 1.132 Declaration of Shai Meretski as showing that a flow system bioreactor is needed to support 3-D stroma cells to allow HSCs expansion when compared with a static system without flow. However, as noted above, Naughton et al can use continuous flow of culture medium, and does not have to use a static system. Use of the fibrous matrix of Sussman et al would have been obvious for its expected advantages, and since it is capable of use in a flow through system for cell culture. When using continuous flow of medium as disclosed by Naughton et al, a difference in results as shown by the declaration would not be obtained. Continuous medium flow is obviously going to provide more nutrients to the cells and

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better removal of waste products, and result in more cell growth than when using static conditions. While the declaration describes the flow reactor apparatus in detail, it does not describe in detail the static reactor apparatus used, and the type of static reactor used would influence the difference in results obtained. Furthermore, the flow reactor used contained four parallel units as shown by Figure 1. The reactor of the claims can differ substantially from that of Figure 1, and would not have to produce results when using the reactor of the figure.

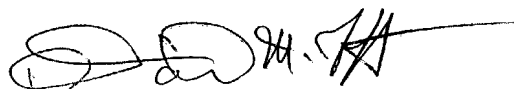
#### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is 571-272-0920. The examiner can normally be reached on Monday-Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



David M. Naff  
Primary Examiner  
Art Unit 1651

DMN  
4/5/04